Molecular Targeted Therapies for Head and Neck Cancer: A New Era in DNA-based Therapeutics

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Over the past decade, the field of cancer therapeutics has slowly moved towards selective molecular targeting of oncogene addicted tumors. Inhibition of molecules overexpressed in or critical for vital mechanisms in cancer cells should theoretically induce selective tumor cell death. Head and Neck Squamous Cell Carcinoma (HNSCC) is the 6th most common cancer world-wide. The front runner in molecular targets for HNSCC has been the Epidermal Growth Factor Receptor (EGFR), although other targets are also being developed in the light of low clinical outcomes using single agent EGFR inhibitors including cetuximab and erlotinib.

Even as the search for EGFR inhibitors with higher efficacy continues, DNA-based approaches including EGFR antisense gene therapy are demonstrating promising results in clinical trials. A plasmid DNA expressing antisense EGFR injected intratumorally in HNSCC patients in a phase 1 setting demonstrated a clinical response in 29% of patients with reduction in tumor EGFR levels post treatment [1]. The treatment was well tolerated by patients. Other molecules downstream of receptor tyrosine kinases that may prove useful as targets include PLCγ-1, phosphoinositol-3 kinase (PI-3K), Src family kinases, mammalian target of rapamycin (mTOR) and signal transducers and activators of transcription (STATs). Among the STATs, STAT3 in particular is reported to be upregulated and constitutively activated by EGFR in HNSCC primary tumors. In a highly innovative study, a double stranded DNA based decoy approach targeting STAT3 was tested in a phase 0 clinical setting [2]. Intratumoral administration of the STAT3 decoy resulted in a reduction of target gene expression indicating that the decoy was effective in blocking STAT3 function within the tumor cells. DNA-based agents are also attractive as vaccines. A DNA construct encoding human papilloma virus (HPV) E7 antigen is being tested for efficacy in enhancing T-cell-mediated antitumor immune responses in HPV-related HNSCC tumors (clinicaltrials.gov identifier NCT01493154).

Critical aspects in the development of DNA-based molecular inhibitors, is to achieve serum stability and tumor-uptake of the agent, identify the best suited patient population and to have measurable responses to therapy. Ideally patient screening would involve confirmation of the oncogenic dependence of the individual’s tumor to the particular molecular target being tested. Response to therapy can be measured at the macroscopic level, wherein the tumor size and degree of cellular differentiation are examined or at the molecular level, where levels of target biomarkers are quantified. Although there have been just a handful of studies using DNA-based agents for the treatment of HNSCC, the results have been promising enough to encourage the development of DNA-based agents that can be systemically delivered to specifically target HNSCC tumors.

References